Review Article

# LIMITATIONS OF CURRENT APPROACHES FOR THE TREATMENT OF ACROMEGALY

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## ABSTRACT

***Objective:*** Acromegaly is a rare disease characterized by hypersecretion of growth hormone (GH), typically from a benign pituitary somatotroph adenoma, that leads to subsequent hypersecretion of insulin-like growth factor 1 (IGF-1). Patients with acromegaly have an increased risk of mortality and progressive worsening of comorbidities. Surgery, medical therapy, and radiotherapy are currently available treatment approaches for patients with acromegaly, with overall therapeutic goals of lowering GH levels and achieving normal IGF-1 levels, reducing tumor size, improving comorbidities, and minimizing mortality risk. Although surgery can lead to biochemical remission in some patients with acromegaly, many patients will continue to have uncontrolled disease and require additional treatment.

***Methods:*** We reviewed recently published reports and present a summary of the safety and efficacy of current treatment modalities for patients with acromegaly.

***Results:*** A substantial proportion of patients who receive medical therapy or radiotherapy will have persistently elevated GH and/or IGF-1. Because of the serious health consequences of continued elevation of GH and IGF-1, there is a need to improve therapeutic approaches to optimize biochemical control, particularly in high-need patient populations for whom current treatment options provide limited benefit.

***Conclusion:*** This review discusses current treatment options for patients with acromegaly, limitations associated with each treatment approach, and areas within the current treatment algorithm, as well as patient populations for which improved therapeutic options are needed. Novel agents in development were also highlighted, which have the potential to improve management of patients with uncontrolled or persistent acromegaly. **(Endocr Pract. 2016;22:210-219)**

**Abbreviations:**
**AACE** = American Association of Clinical Endocrinologists; **AE** = adverse event; **ATG** = Autogel; **CFRT** = conventional fractionated radiotherapy; **DA** = dopamine agonist; **ENDO** = Endocrine Society; **GH** = growth hormone; **GHRA** = growth hormone receptor antagonist; **IGF-1** = insulin-like growth factor 1; **LAR** = long-acting release; **LFT** = liver function test; **SC** = subcutaneous; **SRS** = stereotactic radiosurgery; **SSA** = somatostatin analogue; **sst** = somatostatin receptor; **$sst_2$** = somatostatin receptor subtype 2; **$sst_5$** = somatostatin receptor subtype 5; **TSS** = transsphenoidal surgery.

## INTRODUCTION

Acromegaly is a rare hormonal disease caused primarily by hypersecretion of growth hormone (GH) from benign pituitary somatotroph adenomas. Although it is rare, acromegaly can also be caused by secretion of ectopic growth hormone-releasing hormone (1). Excess GH induces hepatic production of insulin-like growth factor 1 (IGF-1), leading to regulation of cell proliferation and differentiation, cytoskeletal changes, and glucose metabolism alterations (2). Acromegaly has a prevalence of 36 to 69 cases per million, with a prevalence upwards of 115 to 295 cases per million having been reported (3), and an incidence of 3

Submitted for publication May 17, 2015
Accepted for publication September 17, 2015
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Published as a Rapid Electronic Article in Press at http://www.endocrinepractice.org on October 5, 2015. DOI:10.4158/EP15825.RA
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to 4 new cases per million per year (4,5). Clinical manifestations observed in patients with acromegaly stem primarily from chronic elevation of GH and IGF-1 (Table 1) (6,7), with prolonged exposure associated with increased mortality risk (8) and decreased overall health-related quality of life (7).

## Complexities in Diagnosis

Early diagnosis and effective therapy are critical to improving clinical symptoms and reducing mortality risk in patients with acromegaly. However, the average time to diagnosis is approximately 10 years due to the insidious onset of symptoms, slow disease progression, overlap of clinical manifestations with other common medical conditions, and difficulties in disease recognition among healthcare providers (9,10). The initial diagnosis of acromegaly is determined by high clinical suspicion, radiologic imaging, and biochemical testing assessed with serum IGF-1 and glucose-suppressed GH (11). Clinical guideline recommendations for biochemical diagnosis of acromegaly are currently available from the American Association of Clinical Endocrinologists (AACE) and the Endocrine Society (ENDO) (Table 2). Evaluation of both GH and IGF-1 is recommended, as they provide a more accurate measure of tumor activity and overall disease activity (12).

**Table 1**
**Clinical Manifestations of Acromegaly Association with Chronic GH and IGF-1 Hypersecretion[a]**

| |
|---|
| **Systemic complications** |
| Arthralgia<br>Bone overgrowth<br>Cardiac hypertrophy<br>Carpal tunnel syndrome<br>Colonic polyps<br>Hypertension<br>Sleep apnea<br>Type 2 diabetes |
| **Tumor mass effects** |
| Cranial-nerve palsies<br>Headaches<br>Vision loss |

Abbreviations: GH = growth hormone; IGF-1 = insulin-like growth factor-1.
[a] Adapted from (60).

## Treatment Goals

Given the serious consequences of long-term exposure to elevated hormone levels, the primary goal of therapy is to achieve biochemical control by reducing GH and normalizing IGF-1 (6,11,13). AACE guidelines define controlled acromegaly as a random GH <2.5 ng/mL and a normal age-matched IGF-1 (11), while ENDO guidelines define it as a target goal of random GH <1.0 ng/mL and an age-matched IGF-1 (13). Other key goals of treatment include controlling tumor mass, improving symptoms, managing comorbidities, and minimizing long-term mortality risk (6,11,13).

## Current Treatment Options and Need for Improved Therapeutic Approaches

The achievement of therapeutic goals in patients with acromegaly relies on surgery, medical therapy, and/or radiotherapy. Although these treatment options have varying success rates for disease control, a multimodal approach can offer effective treatment for many patients, with corresponding improvements in comorbidities, outcomes, and survival (14).

### *Surgery*

Transsphenoidal surgery (TSS) is the mainstay of treatment and is recommended as first-line treatment (11,15). Sinonasal complications such as nasal congestion, changes in taste or smell, sinusitis, and epistaxis are the most frequently reported adverse events (AEs) associated with surgery (16). A key determinant for effective surgery is the experience level of the neurosurgeon, as it is associated with higher remission rates and limited postoperative complications (11,17). Another determinant of surgical success is tumor size. Approximately 75% of patients

**Table 2**
**Clinical Guideline Recommendations for Biochemical Diagnosis of Acromegaly**

| AACE (11) | ENDO (13) |
|---|---|
| • Diagnosis confirmed by GH levels >1 ng/mL after an OGTT<br>• Diagnosis confirmed by elevated IGF-1 levels using age-matched control<br>• Nadir GH threshold of 0.4 ng/mL should be considered | • Measuring serum IGF-1 recommended for a patient with pituitary mass<br>• Random GH levels should not be used for diagnosis<br>• In cases of elevated or equivocal serum IGF-1, diagnosis should be confirmed by lack of suppression of GH to <1 μg/L following an OGTT |

Abbreviations: AACE = American Association for Clinical Endocrinologists; ENDO = Endocrine Society; GH = growth hormone; IGF-1, insulin-like growth factor 1; OGTT = oral glucose tolerance test.

present with a macroadenoma, and these individuals have worse surgical outcomes (11,18). To assess the effectiveness of surgery, AACE and ENDO clinical guidelines recommend a repeated oral glucose tolerance test and repeated measurement of serum IGF-1 at 12 weeks for detection of persistent and recurrent disease (11,13). At a minimum, postoperative IGF-1 should be measured annually (11).

Surgical debulking of pituitary adenomas offers the highest rates of biochemical remission, with higher remission rates observed in patients with noninvasive microadenomas (approximately 80%) than invasive macroadenomas (<50%) (11,17). However, complete surgical removal of the tumor may not be possible in most patients with invasive macroadenomas, and subsequent surgeries provide limited additional benefit (19). Furthermore, many patients will continue to have residual tumors with persistent disease following TSS, and up to 20% will develop recurrent disease within 5 to 10 years after achieving postoperative biochemical remission (20). This underscores the need for improved therapy in these patients to achieve long-term biochemical control.

### *Medical Therapy*

Medical therapy is a recommended treatment option for patients failing to control GH and IGF-1 hypersecretion following TSS and for those who are poor surgical candidates or unwilling to undergo surgery (11,13). Medical therapies are typically used adjuvantly and provide biochemical remission in many patients with persistent or recurrent disease. There are currently 3 main classes available: somatostatin analogues (SSAs), dopamine agonists (DAs), and GH-receptor antagonists (GHRAs) (Fig. 1).

### *Somatostatin analogues*

Somatostatin is a hormone that binds to somatostatin receptors (ssts) in various tissues and inhibits hormone secretion, including GH (21). Somatostatin analogues, considered the mainstay of medical therapy for acromegaly, target pituitary somatotroph tumors and mimic the inhibitory effects of endogenous somatostatin on GH (2). Octreotide short-acting release, octreotide long-acting release (LAR), lanreotide Autogel (ATG), and pasireotide LAR are currently available SSAs approved by the Food and Drug Administration (FDA) for treatment of acromegaly in the U.S. (22-25). Octreotide LAR, lanreotide ATG, and pasireotide LAR are long-acting formulations available for patients requiring long-term use and control. Pituitary somatotroph adenomas express relatively higher levels of subtypes 2 and 5 ($sst_2$ and $sst_5$) (2,21,26). Octreotide and lanreotide are first-generation SSAs that target and bind with higher affinity to $sst_2$ (27). By contrast, pasireotide is a next-generation, multireceptor-targeted SSA with high binding affinity to $sst_5$ (22).

According to AACE and ENDO guideline recommendations, patients with acromegaly treated with SSAs should be monitored for disease activity by assessing both

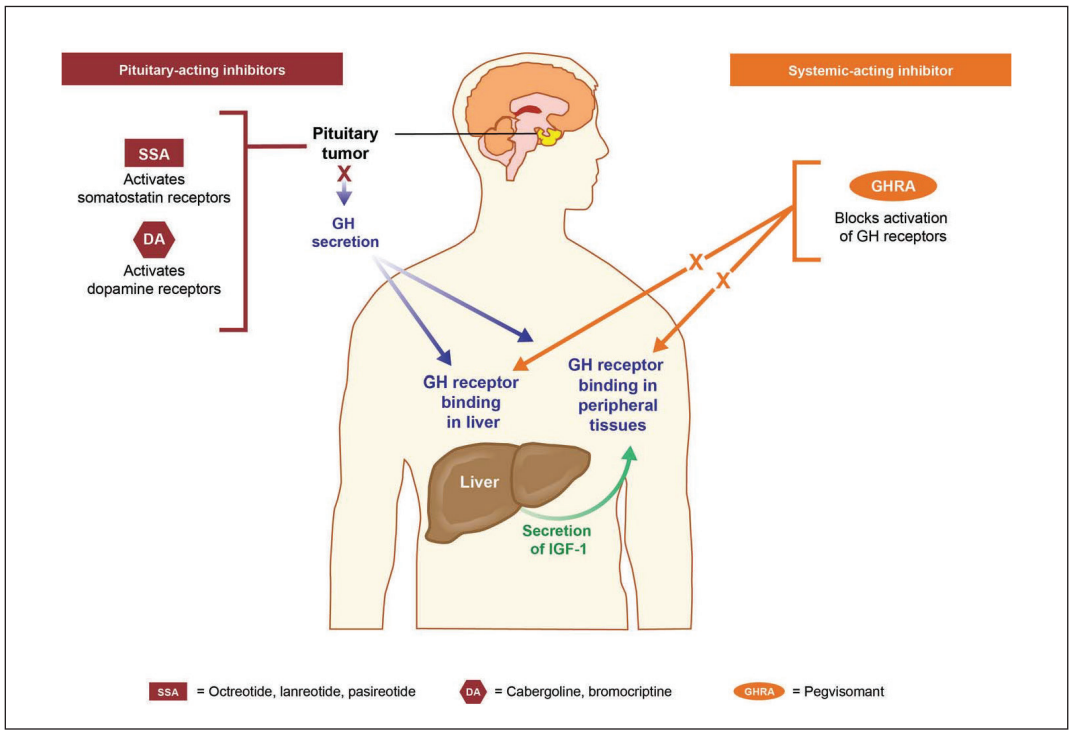


**Fig. 1.** Classes of medical therapies for the treatment of patients with acromegaly. *DA* = dopamine agonist; *GH* = growth hormone; *GHRA* = growth hormone receptor antagonist; *IGF-1* = insulin-like growth factor 1; *SSA* = somatostatin analogue.

GH and IGF-1, and IGF-1 should be measured 3 months after administration of a new dose of a long-acting SSA (11,13). However, there is no additional specific guidance on the frequency of GH and IGF-1 testing for patients treated with SSAs. In meta-analysis studies, octreotide LAR and lanreotide ATG provided biochemical control to 50 to 70% of patients with active acromegaly, and tumor shrinkage was observed in 40 to 90% (28,29). Most AEs associated with SSAs were mild to moderate in intensity and were related to injection-site discomfort and gastrointestinal disturbances (i.e., abdominal pain, diarrhea, nausea, and vomiting) (30). However, while a large proportion of patients are controlled by SSAs, up to 45% do not achieve biochemical control with SSA monotherapy (31). This indicates that benefit is limited for many patients treated with SSAs and highlights the need for improved options for achieving long-term disease control.

***DAs***

DAs bind selectively to dopamine-2 receptors expressed on somatotropic pituitary cells (32). Two agents, bromocriptine and cabergoline, are approved for treatment of acromegaly. Similar to SSAs, disease activity after therapy with DAs is monitored by long-term assessment of both GH and IGF-1. However, the only guidance provided by AACE regarding monitoring is measurement of GH, prolactin, and IGF-1 levels 4 to 6 weeks after a dose change (11). Bromocriptine is rarely used because it is associated with high incidence of side effects and has limited effectiveness in achieving biochemical control despite its use at high doses (32,33). Cabergoline is a more widely used DA that induces biochemical remission in many patients with better tolerability than bromocriptine (11,32). In clinical studies, reduced GH and/or normal IGF-1 were reported in approximately 50% of carbergoline-treated patients, with variable effects on tumor size (34,35). It is generally accepted that DAs are less effective than SSAs in achieving biochemical control (36); therefore, the recommended use of DAs is limited to patients who have mild disease (modest elevations in GH and IGF-1) (11,13) and those whose disease is uncontrolled by SSAs (11). Commonly reported AEs associated with dopamine agonists include gastrointestinal discomfort, headaches, and hypotension. Cardiac valve disease has been reported with high doses of cabergoline in Parkinson's disease; however, whether this event occurs in patients with acromegaly remains unclear.

***GHRAs***

Pegvisomant is a GHRA that is indicated for patients with acromegaly who have inadequate response to surgery or radiation therapy or for whom these therapies are not appropriate (11,37). Unlike SSAs and DAs, pegvisomant does not target pituitary somatotroph tumors and does not reduce GH production. Rather, pegvisomant blocks the effects of excess GH, resulting in decreased IGF-1 (38). In early clinical studies, pegvisomant normalized serum IGF-1 in 76 to 97% of patients (39-42). However, a more recent study reported that 63% of patients achieved normal IGF-1 levels with pegvisomant (43). This reported efficacy rate is lower than in previous studies, which can potentially be attributed to inadequate dosing, different criteria used to define or assess normal IGF-1, and/or lack of adherence to therapy (43). Because GH secretion is not inhibited by pegvisomant, it is unsuitable as a marker for disease monitoring, and only IGF-1 assessment is recommended to measure disease control (11,13). Currently, there are no specific guidelines on the frequency of IGF-1 testing in patients treated with pegvisomant (39-42). AACE and ENDO guidelines recommend regular monitoring for pituitary tumor growth (11,13) because tumor enlargement has been reported in patients treated with pegvisomant (41). However, these results are unconfirmed, and changes in tumor volume are not considered clinically significant (44). Abnormal liver function test (LFT) results are one of the most commonly reported AEs, and approximately 5% of patients treated with pegvisomant have been reported to have transaminase levels threefold greater than normal (11). In some cases, improved LFTs have been observed with continuation or discontinuation of treatment. Nevertheless, results of LFTs should be regularly monitored in patients requiring long-term use of pegvisomant (11).

***Combination therapy***

Multiple studies have been conducted to evaluate effects of combining approved medical therapies in an effort to develop more effective therapeutic options (45-47). Combination therapy may be effective for patients who have lost a response, have exhibited a partial response, or did not achieve a response to SSA monotherapy (11,13). Frequent monitoring of GH and IGF-1 is recommended for patients receiving combination therapy; the emphasis on monitoring one or both of these hormones depends on the medical agent(s) used (11). However, there is no specific guidance on the frequency of GH and IGF-1 testing in patients treated with combination therapy.

Although examined in a few small clinical studies, combination therapy produces significant biochemical remission in uncontrolled patients. Cabergoline with an SSA (octreotide or lanreotide) was reported to improve GH response and normalize IGF-1 in 42% of patients who were uncontrolled following SSA monotherapy (47). In separate studies, 68% achieved normal IGF-1 with cabergoline plus low-dose pegvisomant (45), while 95% met biochemical endpoints with SSAs plus low-dose pegvisomant (46). Additionally, combination therapy with SSAs plus varying doses of pegvisomant provided normalization of IGF-1 levels in 56% of patients with aggressive acromegaly and poorly controlled IGF-1 (48). Thus, dose adjustment of pegvisomant alone or in combination was

critical to achieve optimal biochemical control, particularly with longer duration of treatment.

A treatment algorithm for the medical management of patients with acromegaly was recently proposed that describes appropriate scenarios for the use of combination therapy (6). Despite significant benefits in uncontrolled patients, combination therapy does not provide control for all patients and has the additional burdens of requiring more complex treatment regimens, potentially increasing healthcare costs and exacerbating AEs due to the administration of multiple drugs to patients with high comorbidity burdens.

### *Radiotherapy*

Conventional fractionated radiotherapy (CFRT) and stereotactic radiosurgery (SRS) are used adjuvantly for patients who experience residual disease following surgery (17,49), respond inadequately to primary medical therapy (6,11,13), or fail surgery and medical therapy. While AACE guidelines do not provide specific recommendations for monitoring of hormone levels during radiotherapy (11), ENDO guidelines recommend annual reassessment of GH and IGF-1 following withdrawal from medical therapy to monitor efficacy of radiotherapy (13). The effectiveness of CFRT for achieving biochemical remission is largely limited and variable (49). The maximum response rate for reduction of GH after 1 year of CFRT is 30 to 50%, with an average reduction of 10 to 15% observed thereafter (50). The response to CFRT is typically delayed up to 10 years (51) and is associated with higher risks of developing hypopituitarism and long-term cognitive defects (16). Additionally, there is an increased risk of mortality (52) and of developing radiation-induced secondary tumors such as glioma or meningioma (53). However, clinical studies of SRS with gamma knife surgery (GKS) have demonstrated that this technique is associated with quicker biochemical remission and lower rates of hypopituitarism than CFRT (49,54). Other forms of SRS such as cyber knife therapy may offer clinical advantages similar to those of GKS over CFRT. Given the AEs associated with CFRT and SRS and the variable times required to achieve control, these treatment options may have more limited value for patients who fail to achieve biochemical remission following TSS and/or medical therapy.

## Impact of Therapy on Clinical Outcomes

Current therapies have significant effects on clinical outcomes in patients who achieve biochemical control, as it is associated with reducing mortality risk, achieving mortality rates similar to control populations (55), and improving quality of life and comorbidities (56,57). Specific comorbidities reported to improve with long-term biochemical control include hypertension, sleep apnea, arthralgia, and carpal tunnel syndrome (55,58,59). Despite significant benefits provided by surgical, medical, and radiotherapy approaches, there are diverse subgroups of patients with acromegaly for whom current treatments have limited benefits.

## Are There Acromegaly Patient Populations That Need Improved Therapy?

Significant progress has been made over the past decade in improving clinical outcomes and reducing mortality in patients with acromegaly. However, as discussed earlier, a proportion of patients will continue to have persistent or recurrent disease despite surgical and medical intervention. Thus, despite recent progress, there remain subpopulations of patients with diverse characteristics who require improved therapeutic options.

### *Patients with Delayed Diagnosis or Undiagnosed Disease*

At the time of diagnosis, >50% of patients exhibit clinical manifestations and comorbidities indicative of advanced disease (9). In addition, in large part because of delayed diagnosis, many patients also present with macroadenomas (18) and are exposed for long periods to the damaging effects of GH and IGF-1 hypersecretion without proper diagnosis or appropriate treatment. Thus, it is imperative to improve management strategies that are effective at directing patients into treatment programs. Several factors contribute to the ongoing challenges of early diagnosis, including rarity of the disease, lack of disease recognition, and need for multidisciplinary consultations (9). Therefore, increasing awareness and understanding of disease among healthcare professionals is needed to promote earlier implementation of treatment.

### *Patients Ineligible for Surgery*

While pituitary surgery is highly effective as first-line treatment for many eligible patients, a proportion will be unsuitable for or refuse surgery. They also may have a low probability of surgical cure because of cavernous sinus involvement (11). In these selected cases, primary medical therapy is recommended because of its rapid onset of action.

Primary medical therapy is indicated for patients with unresectable invasive tumors with minimal chance of surgical cure, those with contraindications to surgery, and those who prefer it over other options (11,13,60). Primary medical therapy, often with SSAs, may normalize IGF-1 in up to 70% of patients, with subsequent reductions in tumor volume (60-62). However, up to 50% will not achieve biochemical control after primary therapy with SSAs (63), and combination therapy, shown to be effective in some patients, is recommended (6,11,13). For patients with partial response to SSAs, recommended treatment options include combination SSAs with DAs, or SSAs with pegvisomant. Pegvisomant alone is considered for those having no response with SSAs (6,11,13). Radiotherapy is

recommended for patients who have failed primary medical therapy and combination therapy (11,13). The time to effect and serious AEs associated with radiotherapy are important limitations that need to be considered (52,53).

There is considerable need for improved therapies in this subset of patients. Without improved treatment, they remain at risk for irreversible health effects associated with uncontrolled acromegaly. These patients are uniquely characterized by having intact somatotroph adenomas and would likely benefit from therapies that effectively target their tumor.

### *Patients with Persistent or Recurring Disease after Surgery*

Many patients with acromegaly do undergo surgery, but approximately 40 to 60% do not achieve durable biochemical remission with surgery alone (11,17,18,20). Additionally, approximately 20% will experience recurrent disease following postsurgical remission (20). Medical therapy remains the treatment of choice for postsurgical patients with uncontrolled disease and is associated with long-term biochemical remission. However, multiple national registry studies highlight that up to 26 to 64% of patients receiving postoperative medical therapy remain inadequately controlled (35,64-66). Importantly, a meta-analysis found that 45% of patients will continue to have persistent and uncontrolled disease after surgical and medical intervention (31). As previously mentioned, combination therapy is often used in these patients, but it does not always provide a benefit. Therefore, changes in the current strategy are needed to improve long-term outcomes.

Patients who undergo surgery have the advantage that the source of GH hypersecretion is removed. However, this success is largely dependent on tumor size and expertise level of the neurosurgeon (11,17). In cases of persistent or recurrent disease following surgery, continuing therapy with regular monitoring, increasing dosage of medical therapy, switching to other medical therapy, and using combination medical therapy or radiotherapy are all recommended (6). An unresolved issue in this population is how to achieve higher rates of sustainable biochemical control with available treatment over the long term.

### *Patients Lost to Follow-up*

A substantial proportion of patients achieving biochemical control with medical therapy will require long-term treatment to maintain benefit. Although these patients have controlled disease, active monitoring is required to detect recurrence of disease and sustain beneficial health effects associated with biochemical remission (6). Yet some patients are lost to follow-up and are at an increased risk for active disease. A recent pilot study reported that nearly 1 in 5 patients was lost to follow-up (67). The absence of reported symptoms was the most common patient-reported reason for lack of adherence to follow-up visits, resulting in poor compliance to prescribed therapy, sometimes for up to 5 years. Importantly, 88% of evaluable patients who were lost to follow-up had active disease.

A continuing challenge in management of patients with acromegaly is the long-term nature of care required. Even for patients who achieve biochemical control, optimal management can be compromised if proper monitoring and/or compliance with treatment are not maintained. For patients who are lost to follow-up, there is a need for improved management because current therapies may only be effective if continuity of care is maintained.

## New Therapies for Treatment of Acromegaly

The diversity of patient subgroups with uncontrolled acromegaly highlights a need for improved therapies. Several novel medical therapies have been evaluated in recent years.

### *Pasireotide LAR*

Pasireotide LAR is a next-generation, multireceptor-targeted SSA recently approved by the FDA for treatment of patients with acromegaly who have had inadequate responses to surgery and/or for whom surgery is not an option (22). In a prospective phase 3 study, pasireotide LAR demonstrated superior efficacy over octreotide LAR in medically naïve patients with acromegaly (68). A significantly higher proportion of patients achieved biochemical control with pasireotide LAR (31.3%) than with octreotide LAR (19.2%) (68), and suppression of hormone markers by pasireotide LAR was maintained for up to 25 months (69). Patients treated with pasireotide LAR showed improvement in symptoms and a safety profile similar to those treated with octreotide LAR, except for a higher frequency of hyperglycemia (28.7% vs. 8.3%).

In a second phase 3 study, pasireotide LAR showed superiority over continued treatment with octreotide LAR and lanreotide ATG in inadequately controlled patients (70). Treatment with pasireotide LAR decreased mean values of GH and IGF-1 from baseline to week 12, and these values remained stable through week 24. By contrast, mean IGF-1 levels remained close to baseline and mean GH levels decreased slightly in patients who continued on octreotide or lanreotide. Pasireotide LAR also demonstrated higher rates of tumor volume reduction than octreotide LAR or lanreotide ATG. The safety profiles were similar, except for higher frequency of hyperglycemia with pasireotide LAR (pasireotide LAR 40 mg, 33%; pasireotide LAR 60 mg, 31%; active control, 14%). In addition to its superior efficacy in medically naïve patients, pasireotide LAR may be an effective medical therapeutic option for patients who failed to achieve biochemical control with currently approved SSAs (22).

### *Somatoprim*

Somatoprim is a novel SSA currently under investigation for treatment of acromegaly. Somatoprim binds to $sst_2$, $sst_4$, and $sst_5$ and has been reported to be more potent than octreotide in reducing GH in vitro (71). Notably, somatoprim reduced GH by pituitary adenomas in patients who did not respond to octreotide and is reported to have less effect in decreasing insulin secretion (71,72). These preliminary data suggest that somatoprim could become a new medical therapy for uncontrolled patients.

### *Octreotide Subcutaneous Depot*

Octreotide subcutaneous (SC) depot is currently being developed as a long-acting octreotide for treatment of acromegaly. Octreotide SC depot is administered SC as a low-volume injection and uses a proprietary FluidCrystal® Injection depot (Camurus AB, Lund, Sweden) that allows for controlled release of octreotide over extended periods. In healthy volunteers, octreotide SC depot was well tolerated and significantly reduced IGF-1 after a month of treatment (73). Further studies are currently under way to evaluate octreotide SC depot as a potential treatment for acromegaly.

### *Oral Octreotide*

A novel formulation currently under clinical investigation for acromegaly is oral delivery of encapsulated octreotide (74). In a recently completed phase 3 study, 65% and 62% of evaluable patients who were switched from injectable SSAs and treated with oral octreotide achieved the primary endpoint (age-matched IGF-1 <1.3 × upper limit of normal and GH <2.5 ng/mL) by month 7 and up to 13 months, respectively, compared with 88.7% of patients at baseline who were receiving injectable SSAs. Reported AEs in this study were consistent with those associated with SSAs. Thus, oral octreotide might be a viable treatment option and could provide a potential benefit of delivery convenience associated with oral administration.

### *Temozolomide*

Temozolomide, an alkylating chemotherapeutic agent, has been used for the treatment of aggressive pituitary adenomas when other therapeutic options have failed (75). Among 30 cases of pituitary adenomas treated with temozolomide, including 2 cases of GH-producing adenomas, response rates of up to 60% were reported. The future role of temozolomide in the treatment of acromegaly remains to be determined.

## CONCLUSION

Surgery, medical therapy, and radiotherapy each have a proven role in improving clinical outcomes and survival for many patients with acromegaly who achieve biochemical remission. Conversely, some patients will inadequately respond to current treatment options, giving rise to patient subgroups with high need for improved management options (Fig. 2). Currently, high-need patients include those who are undiagnosed and experience long-term effects of GH and IGF-1 hypersecretion, those who do not undergo surgery and have intact adenomas, those who undergo surgery but have persistent or recurrent disease after surgery and medical therapy, and those who have responses to current therapy but not proper follow-up. Without improved management and therapeutic options, these patients will continue to suffer irreversible health effects, worsening of comorbidities, reduced health-related quality of life, and increased mortality risk associated with acromegaly. Multiple novel targeted agents are currently being evaluated. In conjunction with new permutations for combination therapy, therapy switch, optimal dosing, and improved diagnosis and monitoring, these therapies may

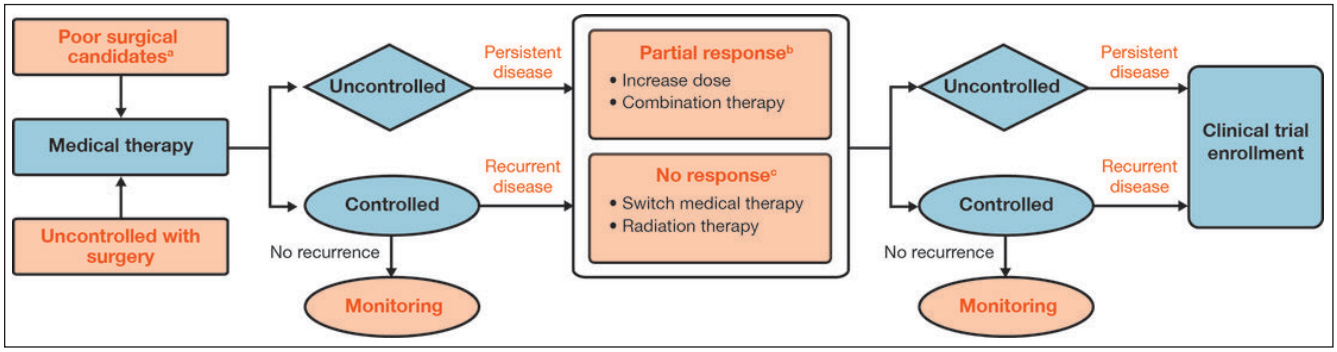


**Fig. 2.** Steps within the current treatment algorithm for acromegaly with potential for improvement (7,12,14). *GH* = growth hormone; *IGF-1* = insulin-like growth factor 1.

[a] Poor surgical candidates are defined as patients with high surgical risk (advanced age, debility, or significant comorbidities), low probability of surgical cure due to extensive tumor spread, or those unwilling to undergo surgery (12,17).

[b] Partial response is defined as reduction in GH and IGF-1 levels, although not necessarily to controlled levels (14).

[c] No response is defined as minimal changes in GH and IGF-1 levels after medical therapy (14).

provide better outcomes and improved management of patients with acromegaly.

## ACKNOWLEDGMENT

Financial support for development of this manuscript was provided by Novartis Pharmaceuticals Corporation. Assistance with medical writing and editing was provided under the direction of the author by Paul Cao and Meredith MacPherson, MedThink SciCom, Inc, with support from Novartis Pharmaceuticals Corporation.

## DISCLOSURE

M.H.S. has received research funding from Novartis Pharmaceuticals Corporation.

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